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I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE BY "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADRESSED TO THE ASSISTANT COMMISSIONER FOR PATENTSWASHINGTON, DC, 20231.

Mary Ellen Fiala

(TYPED OR PRINTED NAME OF PERSON MAILING PAPER OR FEE)

Mary Ellen Fiala

(SIGNATURE OF PERSON MAILING PAPER OR FEE)

A RE 31,851

jc598 U.S. PTO 10/21/98

jc525 U.S. PTO 09/176003 10/21/98

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Assistant Commissioner for Patents
Washington, D.C. 20231

REISSUE APPLICATION TRANSMITTAL

Sir:

Transmitted herewith is the application for reissue of U.S. Patent No. 5,219,888, a Utility Patent, which issued on June 15, 1993.

Inventor(s): Andrew S. Katocs, Jr., Elwood Largis, and Sotirios K. Karathanasis
Title: Use of Retinoids for the Treatment of Coronary Artery Disease

1. Specification, claim(s) and drawings(s) (37 C.F.R. § 1.173)

(a) 9 page(s) of specification
1 page of claims
1 page of abstract

(b) 1 sheet(s) of drawing (drawings amended)
X Formal
____ Informal

X No changes in the drawings, upon which the original patent was issued, are to be made. Therefore, in accordance with 37 C.F.R. § 1.174(a), please find attached, in the size required for original drawings:

___ a copy of the printed drawings of the patent
___ a photoprint of the original drawings
X a letter requesting transfer of the drawings from the original patent file to this reissue application is attached.

2. Reissue Declaration and Power of Attorney

__4__ Pages of Reissue Declaration and Power of Attorney

3. Consent by Assignee for Filing of Reissue Application.

4. Establishment of Right of Assignee to Take Action.

5. Assignment from Katocs, Largis and Sotirious to American Cyanamid Company.

6. Offer to surrender the original letters patent in accordance with 37 C.F.R. §1.178 is attached.

_____ Offer to surrender is by the inventor

__X__ Offer to surrender is by the assignee of the entire interest (and the reissue application does not seek to enlarge the claims of the original patent).

7. Letters patent

_____ Original letters patent are attached.

_____ Declaration that original letters patent lost or inaccessible is attached.

__X__ A copy of the original printed patent is attached.

8. Information Disclosure Statement

__X__ Attached

__X__ Copies of the IDS citation(s) is/are attached.

9. Basic Filing Fee Calculation (37 C.F.R. 1.16(h), (i) and (j)

CLAIMS AS FILED

Number Filed		Number Extra	Rate	Basis Fee (37 C.F.R. 1.16(h) $790.00
Total Claims	1	0	22.00	0.00
Independent Claims	1	0	82.00	0.00
		Filing Fee calculation		$790.00

10. Total Fees due

Filing Fee $790.00

11. Method of Payment of Fees

_____ Enclosed is a check in the amount of $ _____

__X__ Charge American Cyanamid Company Account No. 01-1300 in the amount of $790.00 .

A duplicate of this request is attached.

12. Authorization to Charge Additional Fees

__X__ The Commissioner is hereby authorized to charge any additional fees by this paper and during the entire pendency of the application to American Cyanamid Company Account. No. 01-1300.

Respectfully submitted,

Rebecca R. Barrett

Rebecca R. Barrett
Reg. No. 35,152

Dated: October 21, 1998
Telephone: (610)-902-2646

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Application of:	)	**Examiner:** Kimberly R. Jordan
U. S. Patent No. 5,219,888 Issued June 15, 1993	)	**Group Art Unit:** 1205
ANDREW S. KATOCS, JR., **ELWOOD LARGIS,** **And SOTIRIOS K. KARATHANASIS**	)	
Application No.: 07/860,814	)	
Filed: March 31, 1992	)	
For: Use of Retinoids for the Treatment Of Coronary Artery Disease	)	

ESTABLISHMENT, UNDER 37 C.F.R. §3.73(b), OF RIGHT OF ASSIGNEE TO TAKE ACTION

Sir:

Pursuant to 37 C.F.R. §3.73(b), American Cyanamid Company hereby establishes ownership of the entire right, title and interest in the above-identified Letters Patent and the subject application for reissue thereof by specifying that such ownership was acquired by assignment from the inventors, Andrew S. Katocs, Jr., Elwood Largis, and Sotirios K. Karathanasis, recorded May 4, 1992, on the assignment records of the U.S. Patent and Trademark Office at Reel 6118, Frames 0783-0786. A copy of that assignment as recorded is attached.

AMERICAN CYANAMID COMPANY

Ronald J. Alice

By: Ronald W. Alice
Title: Assistant Secretary
Date: October 20, 1998

USE OF RETINOIDS FOR THE TREATMENT AND PREVENTION OF CORONARY ARTERY DISEASE

Background of the Invention

1. Field of the Invention

The present invention relates to the therapeutic use of retinoids to increase plasma HDL levels for the treatment and prevention of coronary artery disease.

2. Description of the Related Art

High Density Lipoproteins (HDL), a heterogeneous population of spherical particles containing variable amounts of lipids and apolipoprotein, are the most abundant lipoproteins in the plasma. It has recently been observed that low plasma HDL levels are associated with an increased incidence of coronary artery disease (CAD). Numerous epidemiological studies over the last thirty years have verified this association and provided evidence for a putative protective effect of increased HDL levels against CAD: Miller, N.E., *Am. Heart J.* 113:589-597 (1987). It is believed that HDL plays a fundamental role in the lipid transport system and that HDL represents a site for transient storage of potentially harmful lipids and apolipoproteins which, if they were not packaged into lipoprotein particles, might damage cell membranes because of their potential detergent properties; Eisenberg, S., *J. Lipid Res.* 25:1017-1058 (1984).

It is known that high-density lipoproteins are involved in a large number of diverse intravascular metabolic processes including the process of reverse cholesterol transport, in which cholesterol from extrahepatic tissue is transported to the liver for conversion to bile acids and eventual excretion. As a result of these observations, research efforts have focused on methods of affecting plasma HDL levels in order to provide protection against CAD.

As stated above, HDL's are spherical particles containing variable amounts of lipoproteins and apolipoproteins. A polipoprotein A1 (Apo A1) is a major protein constituent of plasma HDL and intestinally derived lipoproteins known as chylomicrons. Although recent studies suggest that dietary, hormonal and other environmental factors regulate apo A1 gene expression, the molecular basis for the mechanisms involved remain poorly understood. It is known that the gene coding for apolipoprotein A1 is expressed predominantly in the liver and intestine. Previous

work has shown that hepatocyte-specific expression is determined by synergistic interactions between transcription factors bound to three separate sites with a powerful liver-specific enhancer located in the region -222 to -110 nucleotides upstream of the apolipoprotein A1 start site; Widom et al., *Mol. Cell Biol.* 11:677-687 (1991). In a recent study, it was found that one of the sites in this enhancer is a highly specific retinoic acid-responsive element (RARE) that responds to recently identified retinoic acid receptors (RXRa); Rottman et al., *Mol. Cell Biol.* 11:3814-3820 (Jul. 1991). These results suggest that retinoic acid response pathways mediated by RXRa play a role in apolipoprotein A1 expression and ultimately cholesterol and retinoid transport and metabolism.

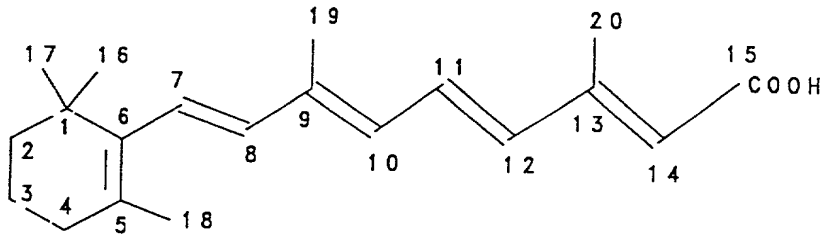
It has been known for many years that retinoids, the family of molecules comprising both the natural and synthetic analogues of retinol (Vitamin A), are potent agents for control of both cellular differentiation and cellular proliferation; Wolbach et al., *J. Exp. Med.*, 42:753-777. Retinoids have been reported to modulate the growth and progression of tumors and premalignant lesions, to affect the immune system, to play a role in inflammatory processes, to regulate differentiation of tissues (especially epithelial) and organs and to influence cellular adhesiveness and cellular interactions. See Pawson et al., *J. Med. Chem.* 25:1269-1277 (1982).

Ringer et al., *Am. J. Chem. Nutr.* 53:688-694 (1991) observed an increase in HDL concentrations in patients given β-carotene, but did not find any changes in apolipoprotein A or B levels. Gollnick et al., Saurat (ed.), Retinoids: New Finds in Research and Therapy, Retinoid Symp. Geneva 1984, pp. 445-460 (Karger, Basel 1985), reported no significant alteration in the HDL and LDL fractions of cholesterol in patients given etretinoate, and a decrease in HDL-cholesterol under isotretinoin. Lyons et al., *Br. J. Dermatology*, 107:591-595 (1982) observed a decrease in HDL-cholesterol levels in patients given 13-cis-retinoic acid.

SUMMARY OF THE INVENTION

The present invention relates to the therapeutic use of retinoids to increase plasma HDL levels for the treatment and prevention of coronary artery disease and to protect against premature atherosclerosis. Suitable therapeutic agents for the practice of this invention include various retinoids. As conventionally defined, retinoids are a class of compounds consisting of four isoprenoid units joined in a head-to-tail manner. All retinoids may be formally derived from a monocyclic parent compound containing five carbon-carbon double bonds and a functional group at the terminus of

the acyclic portion. Representative of these compounds is retinoic acid having the formula:



Although retinoic acid, more particularly transretinoic acid and retinol, more particularly, all transretinoil, are preferred, it is also believed that other retinoid compounds may be successfully used in the practice of this invention to increase plasma HDL levels. Such compounds include all trans-retinoic acid (tretinoin), retinoic acid methyl ester, retinoic acid ethyl ester, phenyl analog of retinoic acid, retinyl acetate, retinaldehyde and 9-cis retinoic acid. These compounds, their chemistry and synthesis, are described in Frickel, F., Chemistry and Physical Properties of Retinoids: THE RETINOIDS, Sporn, Roberts, Goodman, Eds. Academic Press, p. 7-145 (1984).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing the effect of retinoic acid on plasma HDL cholesterol in peanut oil fed rabbits.

DETAILED DESCRIPTION

As stated above, apo A1 is the major protein constituent of plasma HDL. Numerous epidemiologic, genetic and biochemical studies have provided strong support for the concept that high plasma HDL concentrations protect against premature atherosclerosis. Indeed, it has been previously shown that disruption of the apoA1 and nearby apoCIII genes due to a DNA inversion in the genome of certain patients with premature coronary heart disease causes combined apoA1, apoCIII and HDL plasma deficiency and accelerated atherosclerosis; Karathanasis et al., Apolipoprotein Mutants 2, Sirtori et al., (eds.) p. 143-155 (1989). Thus, the observation that there is a direct correlation between apoA1 and HDL plasma levels and hepatic apoA1 mRNA concentrations (Sorci-Thomas et al., J. Biol. Chem. 263:5183-5189 (1988)) and the results of a recent study showing that retinoic acid

transactivates apoA1 gene expression raises the possibility that retinoic acid and other Vitamin A metabolites may play an important role in atherosclerosis prevention. In this context, studies were conducted to determine whether retinoic acid has an effect on plasma HDL levels.

PROTOCOL FOR TEN WEEK ALL TRANS RETINOIC ACID STUDY

Male New Zealand rabbits weighing between 2.0-2.7 kg were placed on rabbit pellets supplemented with 6% peanut oil with and without all trans retinoic acid. The rabbits were fed 125 g of diet daily during the dark cycle such that the average dose of retinoic acid was 11 mg/kg/day for the first 5 weeks of the experiment and 28 mg/kg/day for the next 5 weeks. For the low and high dose of all trans retinoic acid, 2 and 6 g, respectively, were suspended in 600 ml of peanut oil and hand mixed into 10 kg of rabbit pellets. Approximately 10 ml of arterial blood was collected from the major artery of the ear from each rabbit on a weekly basis. The samples were centrifuged at 3000 rpm at 4° C. for 15 minutes. The resultant plasma samples were frozen at -70° C. Upon thawing the samples were analyzed for HDL cholesterol levels and submitted for clinical chemistry determinations. Body weights were monitored on a weekly basis and food consumption on a daily basis. At the end of the study, the rabbits were sacrificed by pentobarbital sodium overdose via the marginal ear vein. Samples of the liver and small intestine were removed and placed in liquid nitrogen and then into a -70°C. freezer. These tissues will be analyzed for the expression of apolipoprotein A1 mRNA. The results of this study are set forth in Table I and Figure I.

TABLE I

Effect of All Trans Retinoic Acid on Plasma Cholesterol Levels in Rabbits Supplemented With Peanut Oil

HDL Cholesterol
(mg/dL±SE)

Treatment	Week 0	1	2	3	4	5	6	7	8	9	10
Control	23±1	30±1	25±1	21±1	20±2	20±2	21±2	18±2	21±2	23±2	19±2
Retinoic Acid[a]	21±1	26±1[b]	28±2	23±2	24±3	27±2[b]	31±2[c]	29±2[c]	30±3[b]	30±2[b]	27±2[b]

[a] 11 mg/kg/day for the first 5 weeks and 28 mg/kg/day for the last 5 weeks

[b] $p<0.05$

[c] $p<0.01$

PROTOCOL FOR THE DOSE RESPONSE STUDY

Male New Zealand rabbits weighing between 2.3-2.9 kg were grouped according to plasma HDL cholesterol and placed on rabbit pellets supplemented with 6% peanut oil with and without all trans retinoic acid for four weeks at four doses. The rabbits were fed 125 g of diet daily during the dark cycle such that the average doses of all trans retinoic acid were 11, 23, 32 and 40 mg/kg/day. For these doses of all trans retinoic acid, 2.3, 4.6, 6.9, and 9.2 g, respectively, were suspended in 600 ml of peanut oil and hand mixed into 10 kg of rabbit pellets. The animals were handled in a manner identical to that described above in the ten week protocol. The results are set forth in Table II.

TABLE II

Effect of All Trans Retinoic Acid on Plasma HDL Cholesterol Levels in Rabbits Supplemented With Peanut Oil

HDL Cholesterol (mg/dL±SE)

Dose mg/kg/day	Week 0	1	2	3	4
0[a]	26±2	28±2	25±3	25±2	21±3
11[a]	25±3	33±3	32±3	31±2	30±3[c]
23[a]	25±3	30±3	31±2	31±2	30±2[d]
32[b]	26±4	33±5	36±6	35±5	30±5
40[a]	25±3	34±4	36±3[c]	35±3[c]	32±4[c]

a n=8

b n=6

c $p<0.05$

d $p<0.01$

The foregoing results show that during the first weeks of the study, plasma HDL cholesterol levels increased transiently in both the control and drug treated groups and then fell back to pre-dose levels in the third week. During the last 5 weeks of the study retinoic acid at an average dose of 28 mg/kg/day but not peanut oil produced a 50% increase in plasma HDL cholesterol levels. During this time

period HDL protein was increased by 15% and phospholipids by 50% in the retinoic acid treated animals. There were no significant increases in plasma triglycerides or LDL-VLDL cholesterol in either control or retinoic acid treated animals Retinoic acid was well tolerated with no effect on food consumption although body weight gain was decreased during the last five weeks of the study. The only anomaly in plasma chemistry was an elevation of alkaline phosphatase levels in retinoic acid treated animals at both doses. Whether the mechanism for the observed increase in plasma HDL cholesterol levels is due to increased transcriptional rates of the apoA1 gene in the retinoic acid treated animals is currently under investigation.

In accordance with the present invention, the retinoids may be administered orally in association with a pharmaceutically acceptable carrier to humans for the treatment or prevention of coronary artery disease or atherosclerosis.

When the compounds are employed for the above utility, they may be combined with one or more pharmaceutically acceptable carriers, for example, solvents, diluents, and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspension containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 0.05 up to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 500 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 1 to 100 mg, preferably from about 2 to 80 mg. Dosage forms suitable for internal use comprise from about 0.5 to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agent, coloring agent, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The compounds may also be encapsulated in liposomes to allow an intravenous administration of the drug. The liposomes suitable for use in this invention are lipid vesicles and may include plurilamellar lipid vesicles, small sonicated multilamellar vesicles, reverse phase evaporation vesicles, large multilamellar vesicles and the like wherein the lipid vesicles are formed of one or more phospholipids such as phosphotidylcholine, phosphatidyglycerol,

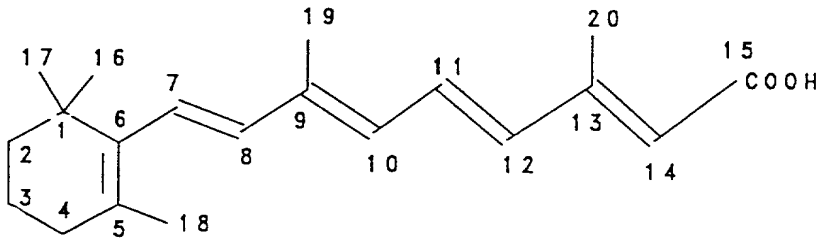
sphingomyelin, phospholactic acid and the like. In addition, the liposomes may also comprise a sterol component such as cholesterol.

We claim:

1. A method of increasing plasma HDL levels in a mammal which comprises administering all-trans-retinoic acid in a pharmacologic amount effective to increase said plasma HDL levels [of a compound selected from the group consisting of the retinoids all trans-retinoic acid, and 9-cis retinoic acid].

ABSTRACT

A method to increase plasma high density lipoprotein levels for the treatment and prevention of coronary artery disease by administering a therapeutic amount of a retinoid of the general formula:



EFFECT OF RETINOIC ACID ON PLASMA HDL CHOLESTEROL IN PEANUT OIL FED RABBITS

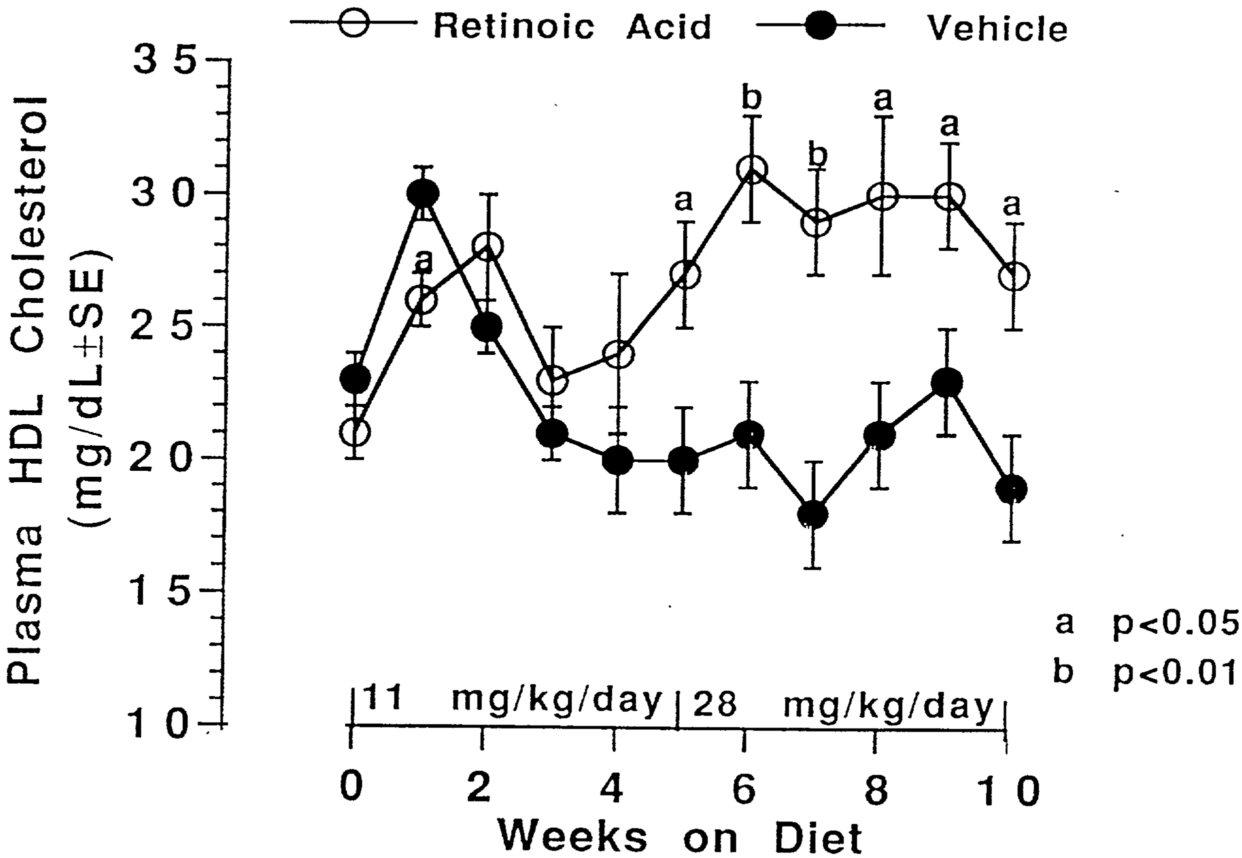


FIGURE 1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Application of:	)	**Examiner:** Kimberly R. Jordan
	)	
U. S. Patent No. 5,219,888	)	
Issued June 15, 1993	)	
	)	**Group Art Unit:** 1205
ANDREW S. KATOCS, JR.,	)	
ELWOOD LARGIS,	)	
And SOTIRIOS K. KARATHANASIS	)	
	)	
Application No.: 07/860,814	)	
	)	
Filed: March 31, 1992	)	
	)	
For: Use of Retinoids for the Treatment	)	
Of Coronary Artery Disease	)	

REISSUE DECLARATION AND POWER OF ATTORNEY BY ASSIGNEE UNDER 37 C.F.R. 1.175

I, RONALD W. ALICE, Assistant Secretary of American Cyanamid Company, declare that:

I am a citizen of the United States of America and resident of Towaco, New Jersey.

The entire title to Letters Patent Number 5,219,888 for Use of Retinoids for the Treatment of Coronary Artery Disease, granted on June 15, 1993 to Andrew S. Katocs, Jr., Elwood Largis, and Sotirios K. Karathanasis is vested in American Cyanamid Company.

I believe said named inventors to be original, first and joint inventors of the subject matter that is described and claimed in the aforesaid letters patent and in the foregoing specification for which invention I solicit a reissue patent.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information that is material to patentability as defined in 37 C.F.R. 1.56. In compliance with this duty, there is attached an information disclosure statement in accordance with 37 C.F.R. 1.98.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

			Priority Claimed	
			Yes	No
NONE				
(Number)	(Country)	(Day/Month/Year Filed)		

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States Provisional Application(s) for Patent listed below:

(Provisional Appln. No.)	(Filing Date)
(Provisional Appln. No.)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status - Patented, pending, abandoned)

I believe the original patent to be partly inoperative or invalid by reason of the patentee claiming more than the patentee had a right to claim in the patent.

More specifically, Interference No. 103,931 was declared between U.S. Patent No. 5,219,888 and U.S. Serial No. 08/482,737 and following an exchange of proof, priority to the use of 9-cis retinoic acid was conceded by Katocs (U.S. Patent No. 5,219,888).

The error listed above, which is being corrected, up to the time of the filing of this reissue declaration arose without any deceptive intent on the part of the applicant.

I hereby appoint the following practitioners to prosecute the application and transact all business in the Patent and Trademark Office connected therewith:

Egon E. Berg, Reg. No. 21,117; Ronald W. Alice, Reg. No. 27,609; of One Campus Drive, Parsippany, New Jersey, 07054; and Thomas J. DesRosier, Reg. No. 30,168; Rebecca R. Barrett, Reg. No. 35,152; Steven R. Eck, Reg. No. 36,126; Arnold S. Milowsky, Reg. No. 35,288; Michael R. Nagy, Reg. No. 33,432; Arthur G. Seifert, Reg. No. 28,040; George Tarnowski, Reg. No. 27,472; all of P.O. Box 8299, Philadelphia, Pennsylvania, 19101; and Daniel B. Moran, Reg. No. 41,204 of 401 N. Middletown Road, Pearl River, New York, 10965.

Address all telephone calls to Rebecca R. Barrett at telephone number (610) 902-2646.

Address all correspondence to Ronald W. Alice, American Home Products Corporation, Patent Law Department - 2B, One Campus Drive, Parsippany, New Jersey, 07054.

I hereby declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Inventor:	Andrew S. Katocs, Jr.
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Name of Inventor:	Elwood Largis
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1937 West Main Street
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~~Thomas DesRosier~~, Assistant Secretary
Ronald W Alice

Assignment recorded in PTO on May 4, 1992,
Reel 6118, Frame 0783-0786

Attached is a STATEMENT UNDER 37 C.F.R. 3.73(b) establishing the right of the assignee to take action in this reissue.

Ronald W. Alice
Title: Assistant Secretary
Date: October 20, 1998